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# Metabolic syndrome as an independent risk factor of hypoxaemia in influenza A (H1N1) 2009 pandemic

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## SUMMARY

A swine-origin influenza A (H1N1) emerged as a pandemic in 2009. We investigated the association between the overweight, metabolic syndrome and the severity of disease in the confirmed cases in Qazvin province, Iran. The study sample included all patients over 12 years old with confirmed influenza A (H1N1) in the province of Qazvin, Iran, in the 2009 pandemic, excluding pregnant women. To define overweight, sex and age-specific body mass index (BMI) cutoffs recommended by the International Obesity Task Force were used. Metabolic syndrome was defined by ATP III criteria. Multiple logistic regression analysis was performed to identify statistically independent predictors of hypoxaemia. Out of 55 confirmed cases, 28 (50.9%) were overweight and 24 (45.3%) were identified as having metabolic syndrome by ATP III criteria. Twenty four patients had hypoxaemia (arterial oxygen saturation below 90%) during the course of the disease. In multivariate logistic regression analysis, pulmonary co-morbidity (OR=9.54; 95% CI, 1.36 to 66.88; p=0.023) and the metabolic syndrome (OR=18.66; 95% CI, 1.60 to 217.47; p=0.019) were revealed to be independent risk factors for hypoxaemia in influenza A (H1N1) pdm09. The results of the present study reveal the role of the metabolic syndrome on the severity of influenza A (H1N1) pdm09 infection.

*Keywords:* metabolic syndrome, influenza, hypoxaemia.

## INTRODUCTION

Metabolic syndrome, which consists of a cluster of metabolically related factors, including central obesity, raised blood pressure, an elevated level of serum triglycerides, decreased level of HDL-cholesterol, and impaired glucose tolerance, was first proposed by Reaven in 1988 and has been well recognized as a powerful predictor of diabetes, and cardiovascular disease morbidity and mortality [1-4].

Increase in abdominal adipose tissue is the most important determinant of metabolic syndrome in developed and developing countries [5, 6]. Moreover, the adipose tissue is now recognized as an immune organ that secretes numerous immunomodulatory factors and seems to be a significant source of inflammatory signals known to cause insulin resistance and alterations in immunologic functions [7].

Most people with metabolic syndrome have higher body mass index (BMI) and are overweighed or obese. Some metabolically obese normal-weight (MONW) individuals despite of having a normal-weight BMI, demonstrate metabolic disturbances. On the other hand, there are some metabolically healthy obese (MHO) individuals with BMI exceeding 30 kg/m$^2$, are relatively insulin sensitive and do not have metabolic syndrome. Therefore these terms should not be considered equivalent [8].

The outbreak of swine-origin influenza A (H1N1) virus that has been called later influenza A (H1N1) pdm09, began in April 2009 and became a pandemic in the subsequent months. That strain

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of H1N1 influenza seems to be highly infectious with low mortality. Higher incidence, in the younger age groups, was one of the most important characteristics of this pandemic and in some investigations up to 60% of patients were under 18 years old.

The first confirmed case of the disease in Qazvin, Iran, was discovered in July 2009 and subsequently 76 additional confirmed cases of infection were detected throughout the entire province [9].

Considering the reports on more severe course of influenza A (H1N1) pdm09 infection in obese persons, inconsistent results in later reports regarding the role of obesity in the prognosis of swine-origin influenza A (H1N1), and observing the more severe hypoxaemia in individuals with central obesity in our hospitalized patients; the present study was designed to investigate the correlation between both overweight and metabolic syndrome and hypoxaemia in the confirmed cases of novel H1N1 influenza in the province of Qazvin, Iran [10-12].

## PATIENTS AND METHODS

*Study design*

This was a cross-sectional study performed in the province of Qazvin (Iran) during July to December 2009. Samples were taken from all patients with clinical symptoms of severe influenza throughout the province of Qazvin. The sampling method and the equipment, primers and probes used for viral RNA extraction and amplification were explained in detail previously [9].

Among the positive cases, those under 12 years, pregnant women or women in the first month after delivery were excluded and the remaining (55 patients) entered the study. Data concerning demographics, occupation and ethnicity were recorded. During a physical examination, blood pressure, height and weight were measured using standardized protocols and calibrated equipment. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters and was rounded to the nearest tenth. Fasting blood sugar, triglycerides, and HDL cholesterol levels were checked and when unavailable, the data were extracted from the patients' medical records. Pulse oxymetry was performed at the first visit for all patients. Patients with tachypnea (regardless of the result of pulse oxymetry) were admitted to province hospitals. Among the hospitalized patients, the lowest percentage of arterial oxygen saturation during the hospitalization period was recorded.

*Definitions*

Hypoxaemia was defined as arterial oxygen saturation less than 90% in pulse oxymetry. Pulmonary co-morbidity was defined as having asthma or chronic obstructive pulmonary disease or other chronic pulmonary disorders.

Overweight was defined as BMI>25 and obesity as BMI>30 in adults. In children and adolescents, standard age and sex specific cutoffs recommended by International Obesity Task Force for overweight and obesity were used [13].

There are various criteria for definition of metabolic syndrome, but the clinical-friendly nature of the National Cholesterol Education Program (NCEP)-Adult Treatment Panel (ATP)-III criteria has caused the widespread use of these criteria in adults and adolescents.

Diagnosis of the metabolic syndrome was accomplished considering the presence of three or more measures of the NCEP Adult Treatment Panel III criteria (waist circumference of greater than 88cm in women and 102 cm in men, arterial blood pressure higher than 130/85 mmHg, serum triglyceride level >150 mg/dL, serum HDL concentration <50 mg/dL for women and <40 mg/dL for men, and fast blood sugar over 110 mg/dL [14].

In younger patients (12-20 years old) the age-specific cutoff points of metabolic syndrome criteria in adolescents that were linked to the NCEP adult criteria were considered [15].

*Statistical methods*

Data were entered in Epi Info 3.5.1 software. Univariate analysis of quantitative data was performed using independent t-test and those of qualitative variables by chi-square and Fisher exact test while the multivariable analysis was accomplished through multivariate logistic regression. A P-value of less than 0.05 was considered to indicate statistical significance.

## RESULTS

In the period between July and December 2009, 76 confirmed cases of new influenza A (H1N1)

**Table 1 -** Demographic characteristics of patients with confirmed influenza A (H1N1) pdm09 infection.

| *Characteristics* | *No./Total No.* | *%* |
|---|---|---|
| **Age group** | | |
| 12-20 yrs | 13/55 | 23.6 |
| 21-50 yrs | 34/55 | 61.8 |
| >51 yrs | 8/55 | 14.5 |
| **Gender** | | |
| Female gender | 24/55 | 43.6 |
| **Occupation** | | |
| Student | 11/54 | 20.4 |
| Teacher | 2/54 | 3.7 |
| Housewife | 16/54 | 29.6 |
| Health Care worker | 2/54 | 13.0 |
| Office employer | 3/54 | 5.6 |
| Military employer | 5/54 | 9.3 |
| Shop keeper | 6/54 | 11.1 |
| Driver | 2/54 | 3.7 |
| Worker | 5/54 | 9.3 |
| Unemployed | 2/54 | 3.7 |

pdm09 infection were discovered in the province of Qazvin. The median age of patients was 23 years and the mean age 25.67±16.9. After excluding those under 12 years and pregnant women, 55 patients entered the study. Demographic, clinical characteristics and laboratory test results are shown in Tables 1 and 2, respectively.

Twenty six (47.3%) patients out of the total were found to have the ATP III criteria associated with metabolic syndrome. Mean of BMI in patients having metabolic syndrome was 28.09±13.61 while in the remaining patients it was 22.48±13.62. (P<0.001) All hospitalized patients (44 cases) were sufficiently ill and tachypneic to put under treatment with oseltamivir and oxygen. Among these patients, 24 had at least one period of arterial oxygen saturation of less than 90% during the course of disease. Overall, 9 cases were admitted to ICUs among those 8 patients needed intubation and eventually 2 patients died. As seen in Table 3, the values obtained for BMI, weight, and waist circumference in hypoxaemic group were significantly higher than nonhypoxaemic patients. Also, it is evident that the factors such as overweight and obesity, underlying pulmonary diseases, neuromoscular disorders and metabolic syndrome were associated with the development of hypoxaemia. These variables were entered in a multivariate regression model with hypoxaemia as the dependent variable. As seen in Table 4, the metabolic syndrome and underlying pulmonary co-morbidities were independently associated with the development of hypoxaemia during the course of infection with influenza A (H1N1) pdm09 virus in Qazvin province, Iran.

## DISCUSSION

Since a long time ago, there have been numerous evidences regarding the role of obesity in the occurrence and severity of infectious diseases. By changing of lifestyle and nutritional habits, the overweight and obesity turned into one of the major problems of human communities [16]. Obesity has been considered as one of the most common causes of mortality and morbidity in developed countries and is turning out to become

**Table 2 -** Clinical characteristics and laboratory test results of patients with confirmed influenza A (H1N1) pdm09 infection, based on gender.

| | *Female* | *Male* | *P-Value* |
|---|---|---|---|
| BMI (kg/m$^2$) | 26.8 ± 5.1 | 23.8 ± 3.8 | 0.017 |
| Height (cm) | 154.2 ± 8.2 | 173.5 ± 9.3 | 0.000 |
| Weight (kg) | 63.3 ± 11.2 | 72.3 ± 14.5 | 0.015 |
| Waist circumference (cm) | 92.7 ± 10.4 | 89.4 ± 9.9 | 0.231 |
| Systolic Blood Pressure (mmHg) | 119.6 ± 15.3 | 124.5 ± 15.5 | 0.245 |
| Diastolic Blood Pressure (mmHg) | 70.8 ± 11.4 | 75.8 ± 10.7 | 0.102 |
| Fasting Blood Sugar (mg/dL) | 100.5 ± 37.5 | 102.2 ± 26.4 | 0.848 |
| Serum triglyceride (mg/dL) | 160.0 ± 74.1 | 158.5 ± 84.8 | 0.909 |
| Serum HDL cholesterol (mg/dL) | 37.3 ± 10.0 | 35.8 ± 7.9 | 0.542 |

**Table 3 -** The relationship between demographic characteristics, underlying diseases and laboratory test results with hypoxaemia in confirmed cases of influenza A (H1N1) pdm09. Data are presented as mean ± SD for quantitative variables or numbers (percentage) for dichotomous variables.

| | *Non hypoxaemic patients (n=31)* | *Hypoxaemic patients (n=24)* | *P Value* |
|---|---|---|---|
| Age (year) | 30.2 ± 14.6 | 34.2 ± 15.9 | 0.343 |
| Gender (female) | 12 (38.7) | 12 (50.0) | 0.402 |
| BMI (female) | 24.2 ± 5.0 | 29.4 ± 4.0 | 0.011 |
| BMI (male) | 22.6 ± 3.2 | 25.9 ± 3.9 | 0.014 |
| Height (cm) | 166.4 ± 11.7 | 166.3 ± 14.6 | 0.386 |
| Weight (kg) | 64.5 ± 13.5 | 73.4 ± 12.7 | 0.017 |
| Waist circumference (cm) | 87.5 ± 10.7 | 95.1 ± 7.6 | 0.005 |
| Diabetes Mellitus | 3 (9.7) | 6 (25.0) | 0.124 |
| Neuromoscular disorders | 1 (3.2) | 6 (25) | 0.022 |
| Cardiac co-morbidity | 3 (9.7) | 1 (4.2) | 0.409 |
| Pulmonary co-morbidity | 2 (6.5) | 15 (62.5) | 0.000 |
| Overweight & obesity | 10 (32.3) | 18 (75.0) | 0.002 |
| Metabolic syndrome | 5 (16.1) | 21 (87.5) | 0.000 |
| Systolic blood pressure (mmHg) | 119.5 ± 15.8 | 126.0 ± 14.5 | 0.122 |
| Diastolic blood pressure (mmHg) | 71.9 ± 11.0 | 75.8 ± 11.2 | 0.202 |
| Fasting blood sugar (mg/dl) | 98.1 ± 31.3 | 105.7 ± 31.7 | 0.380 |
| Serum triglyceride (mg/dl) | 142.0 ± 70.8 | 181.6 ± 86.2 | 0.069 |
| Serum HDL cholesterol (mg/dl) | 38.0 ± 9.0 | 34.5 ± 8.4 | 0.149 |

**Table 4 -** Results of multivariate logistic regression analysis of factors influencing the development of hypoxaemia in influenza A (H1N1) pdm09 throughout the province of Qazvin, Iran.

| | *OR (CI 95%)* | *P value* |
|---|---|---|
| Neuromuscular disorders | 1.77 (0.14-22.92) | 0.6639 |
| Pulmonary co-morbidity | 9.54 (1.36-66.88) | 0.0233 |
| Metabolic syndrome | 18.66 (1.60-217.47) | 0.0195 |
| Overweight & obesity | 0.89 (0.08-10.43) | 0.9240 |

a principal health problem in developing countries [17]. However, it has to be noticed that this increase in the number of cases of overweight and obese individuals shows an uneven distribution throughout the society and there is a considerable variation based on gender, race, and age groups in different countries. In a study carried out in the USA, it was shown that while an increase in obesity of men and children was obvious within a 10 year period no such increase among women established [18]. In contrast, the obesity in women in Iran is turning into one of the major health problems and the rate of obesity among Iranian urban women has become even greater than American women [19]. One of the aspects of this global epidemic is the reciprocal effect of obesity and inflammatory responses. Contrary to our previous belief by which the adipose tissue was known as a place to store energy, currently it has become evident that the adipose tissue is integrally involved in coordinating a variety of biological processes including energy metabolism, neuroendocrine function, and immune function [20]. Similar to malnutrition, that clearly causes the poor function of the immune system, the obesity is also accompanied with functional disorder of the body defense mechanisms and probably increase in mass of adipose tissue induce the chronic aggravation of the pro-inflammatory responses of Th-1 type [21, 22].

The fact that the insulin resistance plays a positive role in improving the function of the immune system during acute infections, could have been accounted as an evolutionary advantage in the past, and perhaps at the present time in communities with high level malnutrition, as in an animal model the higher resistance to cerebral malaria in obese mice has been shown [23, 24].

However, in animal models, the chronic obesity has led to delayed proinflammatory cytokine expression, diminished natural killer cell cytotoxicity, and increased mortality in influenza infection [25]. Moreover, obesity causes poor innate immune response through disrupting the macrophage function in producing an efficient response against bacteria by provoking an appropriate inflammatory reaction [26].

Diet-induced obesity impairs the innate immune response to bacterial infection via a mechanism that damages the ability of their macrophages to respond effectively to bacteria and mount an adequate inflammatory response. Although the course of respiratory diseases in obese individuals is generally more severe and with longer time for recovery [27]. However, it is likely that giving more attention to other risk factors associated with obesity, in particular among aged people, caused the obesity not to be routinely considered among the independent risk factors for occurrence of complications in infection with the other strains of influenza virus [28]. At present, the role of obesity as a risk factor for incidence of severe complications and mortality has become more evident, according to several studies associated with influenza A (H1N1) pdm09 in which the higher incidence of severe complications occurred in over weighted young individuals without co-morbid risk factors [11, 29].

It has to be noted that in previous animal models with acute influenza infection, a decrease in expression of proinflammatory cytokine and natural killer cells and also an increase in mortality of influenza in obese mice has been described. Moreover, high level of leptin in obese mice is reported to have caused leptin resistance, whereas in animal model of influenza infection, compared to underweight mice, not only there was no increase in the level of leptin but a decrease in concentration of leptin was obvious [25]. In the human cases of influenza A (H1N1) pdm09, an increase in concentration of Th-1 and Th-17 cytokines during the acute phase of disease in severely ill patients is reported and in particular high levels of IL-6 and IL-8 cytokines have been associated with more severe disease [30].

Although the real cause of more severe course and increased mortality of influenza in obese persons is not known, but it is clear that the level of leptin, TNF-$\alpha$, IL-6, and IL-1$\beta$ in people with more adipose mass is chronically higher than normal individuals, whereas the concentrations of adiponectin and mannan binding lectin (MBL) are reported to be less than normal persons [7, 31]. Also, it has to be noted that these metabolic changes are mostly due to abdominal fat in particular those of omentum and mesenteric areas [32]. Thus, BMI is only an approximate reflection of adipose tissue mass, and due to the presence of different obesity phenotypes, there is no linear association between BMI and the amount of abdominal fat [8]. This issue that all obese people are not necessarily affected by metabolic syndrome has been suggested long time ago, and even at present, there are many researchers that believe in the existence of fat fit people [33, 34]. This has led to define a new category as metabolically healthy obese (MHO) people, in whom the risk of metabolic complications is at a level between those occurring among people with normal weight and those seen in insulin resistant obese people [35, 36].

In a study carried out on post-menopausal obese women aged 50-71, it was demonstrated that the level of abdominal fat in obese people without metabolic syndrome was 49% less than obese people with metabolic syndrome [37]. In another study, a lower level of both abdominal fat and cardiac intracellular lipid is reported in youngsters without resistance to insulin [38]. Hence, many researchers believe that the obese people with less resistance to insulin have less abdominal fat and occasionally up to 43% of obese people were reported to have resistance to insulin, metabolically [39]. Similarly, there are people at risk of metabolic complications despite having a normal BMI and defined as metabolically obese normal weight (MONW) individuals in whom resistance to insulin as well as abdominal and visceral obesity are generally evident [40].

In our study, a significant correlation between hypoxaemia and BMI was discovered when using univariate analysis. However, when multivariate analysis was employed, our data showed it is the

metabolic syndrome, which is the risk factor for severity of disease and not the BMI. In the first 100 deaths with diagnosis of influenza A (H1N1) pdm09 in Mexico city the prevalence of metabolic syndrome was 39,5 percent compared to 14.5 percent in the general population [41]. In the mentioned study the prevalence for obesity for the two groups were 25.7 and 24.2 percent, respectively. In a case control study performed in 177 hospitals in Brazil, obesity was an independent risk factor of mortality in influenza A (H1N1) pdm09 [42]. In a study carried in Qatar, obesity was not associated with poor outcome in critically ill patients admitted with influenza A (H1N1) pdm09 in intensive care units [43]. In 74 confirmed cases of influenza A (H1N1) pdm09 in Turkey a higher BMI was an independent risk factor for mortality [44]. In our study metabolic syndrome and BMI were strongly associated. It has to be noticed, it is likely that the findings associated with correlation between outcome measures and BMI, in influenza A (H1N1) pdm09 obtained in previous studies, are mostly related to metabolic syndrome rather than BMI, as these variables are strongly associated with each other.

## CONCLUSION

The findings of the present study once again confirm the role of the metabolic syndrome in the course of infectious diseases. Considering the data observed in our study, it is of vital importance to pay more attention to signs and symptoms of influenza in patients with metabolic syndrome and the process of decision making on hospitalization and initiation of antiviral therapy for such patients to be carried out with less scruple. In addition, the interference of metabolic syndrome in statistical analyses associated with risk factors such as intubation, hospitalization in ICUs, and mortality may produce similar results when performed on a larger study population.
The lower number of cases in the province of Qazvin was our most important limitation in generalizing the findings of the present study. Due to the low number of hospitalized cases in ICUs and also low mortality rate, no significant difference between the risk factors and these variables was observed, statistically. Considering a total of only 9 hospitalized patients in ICUs and 2 cases of death, studying the role of the metabolic syndrome in severity of influenza A (H1N1) pdm09 infection clearly needs further investigations on larger study population. Inclusion of metabolic syndrome in statistical analyses associated with risk factors such as intubation, admission to ICUs, and mortality in future studies with larger population size may provide new insights into the possible correlation between metabolic syndrome, obesity, and severity of influenza.

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